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**Comment on 'No major role for glutathione S-transferase gene polymorphisms in sensitization to para-phenylenediamine and other xenobiotics**

Pot, L.M.; Alizadeh, B.Z.; Ahrenberg, D.; Coenraads, P.J.; Snieder, H.; Blomeke, B.

*Published in:*  
BRITISH JOURNAL OF DERMATOLOGY

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2011

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Pot, L. M., Alizadeh, B. Z., Ahrenberg, D., Coenraads, P. J., Snieder, H., & Blomeke, B. (2011). Comment on 'No major role for glutathione S-transferase gene polymorphisms in sensitization to para-phenylenediamine and other xenobiotics: a study of association and a meta-analysis'. *BRITISH JOURNAL OF DERMATOLOGY*, 165(3), 693-694.

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**Comment on 'No major role for glutathione S-transferase gene polymorphisms in sensitization to *para*-phenylenediamine and other xenobiotics: a study of association and a meta-analysis'**

DOI: 10.1111/j.1365-2133.2011.10405.x

MADAM, The correspondence of Pot and colleagues 'No major role for glutathione S-transferase gene polymorphisms in sensitization to *para*-phenylenediamine and other xenobiotics: a study of association and a meta-analysis'<sup>1</sup> may leave the impression that we had argued that glutathione S-transferase (GST) polymorphisms may be generally associated with contact allergy.<sup>2</sup> In fact, we investigated GST polymorphisms in sensitization to mercury-containing compounds such as thiomersal (thimerosal), as thiomersal is exclusively detoxified via glutathione conjugation. We therefore compared thiomersal-sensitized individuals with healthy controls and individuals who were sensitized toward *para*-phenylenediamine. We found that GSTM1 confers a protective effect towards thiomersal and an additive effect concerning GSTT1. We observed no association in the case of *para*-phenylenediamine sensitization. The latter is consistent with the notion that the compound is not predominantly detoxified via the GST conjugation. We concluded that 'Patients sensitized to thiomersal exhibited GSTM1-negative genotypes significantly more frequently than the control group. This seems to reveal a substance-specific association and not a general trait of contact allergic patients, as the more frequent occurrence of the GSTM1 deficiency was not seen in contact allergic patients sensitized against *para*-substituted-aryl compounds. Furthermore the GST allele frequencies in the "thiomersal-group" are not influenced by additional allergies other than phenylmercury or ammoniated mercury chloride. This further supports the concept that the investigation of enzyme polymorphisms may yield allergen-specific genetic markers for increased risk.' We interpret this substance-specific finding as indirect affirmation of the hapten hypothesis. We hope that this clarification will help to avoid further misunderstandings.<sup>3,4</sup>

Ruhr-University Bochum, Institute for Prevention  
and Occupational Medicine of the German Social  
Accident Insurance Institute of the  
Ruhr-Universität Bochum (IPA),  
Bochum, Germany

G. WESTPHAL  
A. SCHNUCH\*

\*University of Göttingen, Information Network of Departments  
of Dermatology (IVDK),  
Göttingen, Germany  
E-mail: westphal@ipa-dguv.de

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Funding sources: none.

Conflicts of interest: none declared.

**Comment on 'No major role for glutathione S-transferase gene polymorphisms in sensitization to *para*-phenylenediamine and other xenobiotics: a study of association and a meta-analysis': reply from authors**

DOI: 10.1111/j.1365-2133.2011.10406.x

MADAM, We would like to thank Westphal and Schnuch for responding to our letter, 'No major role for glutathione S-transferase gene polymorphisms in sensitization to *para*-phenylenediamine and other xenobiotics: a study of association and a meta-analysis'.<sup>1</sup>

As described in their paper, we have acknowledged the fact that Westphal et al.<sup>2</sup> referred to the substrate specificity of thiomersal (thimerosal) for glutathione S-transferase (GST) enzymes. However, both papers used in our meta-analysis also describe the possible role of oxidative stress in sensitization to the studied xenobiotics. Wang et al.<sup>3</sup> suggested that poor GSTT1 activity reduced the protection from reactive oxygen species (ROS) damage and therefore contributed to the occurrence of allergic contact dermatitis to chromate. In addition, Westphal

et al.<sup>2</sup> mentioned the lack of complete understanding of thiomersal allergy and discussed the possibility that the toxicity of thiomersal could have been indirectly related to – among other things – oxidative stress. Moreover, a recently published paper addressed the induction of ROS and CD86 by thiomersal- and mercury analogue-treated monocyte-derived dendritic cells.<sup>4</sup> In general, reduced protection against and subsequent exposure to ROS has been related to contact dermatitis. With the linkage of metabolism of the particular allergens to ROS, and the general linkage of ROS to contact sensitization,<sup>5</sup> we believe that the performed meta-analysis is defensible and justifiable.

Nevertheless, as mentioned in our paper, the differences found in the meta-analysis can be partially explained by the fact that detoxification of the different xenobiotics is dependent on additional factors and cannot be attributed solely to the examined GST genes. This might, as addressed in Westphal and Schnuch's response,<sup>6</sup> particularly be the case for para-phenylenediamine. On the other hand, looking in closer detail actually reveals that results from our study are not that different from those of Westphal et al.<sup>2</sup> They did not find a significant association of the GSTT1 deletion polymorphism with sensitization and only found a relatively moderate odds ratio for GSTM1 deficiency (odds ratio 2.0, 95% confidence interval 1.2–3.4, n = 60 cases), while studying the GST model substrate thiomersal. This suggests that for substrates presumably solely metabolized by GSTs, the effect of GST polymorphisms on sensitization is small. From a substrate specificity perspective, one would then expect that xenobiotics which are not a model substrate and are not solely detoxified by GSTs have an even lower, or no association, as was shown in our study. Hence, we still support our conclusion that common genetic polymorphisms in GSTs seem not to play a major role in predisposition to sensitization.

Department of Dermatology, University Medical  
Centre Groningen, University of Groningen,  
Groningen, the Netherlands

\*Unit of Genetic Epidemiology & Bioinformatics,  
Department of Epidemiology, University Medical  
Centre Groningen, University of Groningen,  
Groningen, the Netherlands

†Department of Environmental Toxicology,  
University Trier,

Am Wissenschaftspark 25–27, 54296 Trier,  
Germany

Correspondence: Brunhilde Blömeke.

E-mail: bloemeke@uni-trier.de

L.M. POT

B.Z. ALIZADEH\*

D. AHRENBURG†

P.-J. COENRAADS

H. SNIEDER\*

B. BLÖMEKE†

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Funding sources: L.M.P. was funded by the Department of Dermatology of the University Medical Centre Groningen, the Netherlands.

Conflicts of interest: none declared.

## Human papillomavirus types 1, 16 and 18 detected in a lesion of verrucous carcinoma of the cheek

DOI: 10.1111/j.1365-2133.2011.10417.x

MADAM, Verrucous carcinoma (VC) is a distinctive form of low-grade squamous cell carcinoma, first reported by Ackerman in 1948.<sup>1</sup> VCs are divided into four groups according to the anatomical site: oral cavity (oral florid papillomatosis), anogenital area (giant condyloma of Buschke and Lowenstein), plantar area (epithelioma cuniculatum) and other cutaneous sites.<sup>2,3</sup> Human papillomavirus (HPV) infection is believed to be a causative factor of VCs of the oral cavity, anogenital and plantar area,<sup>2–6</sup> but has never been detected on the cheek, a very rare site of VC. We describe the first case of VC of the cheek with detection of HPV types 1, 16 and 18.

In June 2009, a 79-year-old Korean woman presented with a 2-year history of a pruritic, keratotic and verrucoid tumour on the right cheek. She had been taking medication for diabetes and hypertension for 20 years. On physical examination, an exophytic, verrucous and hyperkeratotic 3 × 2 cm round tumour was observed on the right cheek (Fig. 1a). An initial superficial punch biopsy of the lesion showed pseudoepitheliomatous hyperplasia with a dense inflammatory cell infiltrate in the dermis. It was difficult to confirm the lesion as VC, so we treated her with a wide excision and a transposition flap.

Histopathological findings of the excised specimen revealed a well-circumscribed tumour that showed marked hyperkeratosis, papillomatosis, acanthosis of the epidermis and a downward bulbous growth of elongated, blunted rete ridges. Hyperplastic epidermis had invaded into the dermis, most likely bulldozing, with keratinocytes that had a ground-glass appearance (Fig. 1b, c). Keratinocyte atypia were few or

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